Remarks

Reconsideration of this Application is respectfully requested.

Upon entry of the foregoing amendment, claims 85-101 are pending in the application, with claims 85 and 88 being the independent claims. Claims 88-100 have been withdrawn. Claims 85 and 86 have been amended to clarify the claim language. As such, these changes are believed to introduce no new matter, and their entry is respectfully requested.

Based on the above amendments and the following remarks, Applicants respectfully request that the Examiner reconsider all outstanding rejections and that they be withdrawn.

Rejections under 35 U.S.C. § 112, first paragraph - written description

The Examiner rejected claims 85-87 and 101 under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter which was not described in the specification to reasonably convey that the inventors had possession of the claimed invention. *See* Office Action at page 2. Specifically, the Examiner alleged

> [w]hilst the specification discloses a particular example of a particular molecule with a particular substitution which apparently has the properties recite[d] in the claims, the claims encompass a vast collection of mutant molecules with the properties recited in the claims that are not disclosed in the specification. It is unpredictable as to what particular substitutions can be made to any particular molecule and result in a mutant analogue molecule with the functional attributes recited in the claims.

Office Action at page 3. Applicants respectfully disagree for the following reasons.

To satisfy the written description requirement, a patent specification must describe the claimed invention in sufficient detail that one skilled in the art can reasonably conclude that the inventor has possession of the claimed invention. *See Regents of the Univ. of Cal. v. Eli Lilly & Co.*, 119 F.3d 1559, 1566 (Fed. Cir. 1997); *see also* M.P.E.P. § 2163. An applicant shows possession of the claimed invention by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams and formulas that fully set forth the invention. *See* M.P.E.P. § 2163, citing *Lockwood v. American Airlines, Inc.*, 107 F.3d 1565, 1572 (Fed. Cir. 1997). "The written description requirement does not require the applicant 'to describe exactly the subject matter claimed'." *Union Oil Co. v. Atlantic Richfield Co.*, 208 F.3d 989 (Fed. Cir. 2000); *see also* M.P.E.P. § 2163.02 ("The subject matter of the claim need not be described literally (i.e., using the same terms or in haec verba) in order for the disclosure to satisfy the description requirement.").

The USPTO's guidelines state:

> [t]he written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species . . . by disclosure of relevant, identifying characteristics, *i.e.*, structure or other physical and/or chemical properties, by functional characteristics . . . or by a combination of such identifying characteristics...

Guidelines for the Examination of Patent Applications Under the 35 U.S.C. § 112, first paragraph, "Written Description" Requirement, 66 Fed. Reg. 1104, 1106.

The specification provides sufficient guidance regarding substitutions of the mutant molecules of the claimed methods.

Applicants respectfully assert that the specification sufficiently details the mutant molecules of the claimed methods. As described in Applicants' Amendment and Reply dated October 31, 2007, the specification describes and illustrates several specific mutant analogs of TNFα (*see, e.g.,* Examples 1-3) as well as methods to make and test mutant analogs for their ability to generate autoantibodies *in vivo* (*see, e.g.,* Examples 3-9). TNF-β, interleukin 1, γ-interferon and IgE are provided as further examples of self-proteins that may be used to generate other mutant analogs (*see, e.g.*, paragraphs [0037]-[0038] of the specification). Therefore, not only does the specification teach examples of self-proteins useful in the invention and methods for making mutant analogs of these self-proteins, but also discloses methods to test the mutant analogs for the asserted activity.

In addition, the specification describes that the substitutions of the self-proteins of the claimed methods can be made using routine genetic engineering methods and preferably induce minimal tertiary structural changes such that the analog induces an antibody response against such self-proteins. *See, e.g.,* paragraph [0031] of the specification. The specification also describes that the fine specificity of the autoantibodies can be regulated by the insertion of the T-cell epitopes at different positions, potentially enabling a turning of the specificity towards a specificity mediating, high neutralizing effect on the desired biological activity. *See, e.g.,* paragraph [0032] and Example 6 of the specification.

Furthermore, the specification describes that recombinant proteins modified according to the claimed methods may be self-immunogenic in large populations

expressing different MHC class II molecules. *See, e.g.*, paragraph [0033] of the specification. The MHC-restriction of the autoantibody response induced was not necessarily confined to that of the inserted T-cell epitope. For example, by modulation of autologous ubiquitin and TNFα according to the present invention, wherein the self-protein analog is produced by substitution of one or more peptide fragments by a corresponding number of peptides known to contain immunodominant T-cell epitopes, it was possible to induce an equally fast and even stronger autoantibody response against TNFα despite the fact that the inserted T-cell epitope used was not restricted to the MHC molecules of the immunized mice. *See, e.g.*, paragraph [0033] and Examples 2-4 of the specification.

Therefore, one of ordinary skill in the art would be able to envision the particular substitutions that can be made to result in the mutant analogs of the claimed methods because the specification describes and illustrates several specific mutant analogs of TNFα as well as methods to make and test mutant analogs for their ability to generate autoantibodies *in vivo*.

Applicants' contention that the written description requirement is satisfied for the present claims is supported by the Federal Circuit's interpretation and application of 35 U.S.C. § 112, first paragraph.

At pages 3-5 of the Office Action, the Examiner alleges that the facts of the present case are similar to those disclosed in *Regents of the University of California v. Eli Lilly (Lilly)*, 119 F.3d 1559 (Fed. Cir. 1997). While Applicants agree that the *Lilly* case involved claims directed to a genus of DNA species encoding insulin wherein only a single species of cDNA was described, Applicants respectfully remind the Examiner

that the present claims are directed to *methods* of inducing autoantibodies against a pathogenic self-protein, not to a genus of pathogenic self-proteins.

According to the Federal Circuit, the disclosure of a patent must allow one skilled in the art to visualize or recognize the identity of the subject matter of the claim. *See id.* at 1568. The specification describes and illustrates several specific mutant analogs of TNFα as well as methods to make and test mutant analogs for their ability to generate autoantibodies *in vivo*. In view of these factors, a skilled artisan would be able to clearly visualize and recognize the methods encompassed by the present claims.

Furthermore, the court in *Enzo Biochem Inc. v. Gen-Probe Inc.* noted that the written description requirement can be met if a functional characteristic is coupled with a disclosed correlation between the function and a structure that is sufficiently known or disclosed. 196 F.3d 1316, 1324-25 (Fed. Cir. 2002). Applicants' claims meet this test.

First, as indicated by the Examiner, the claims recite a functional limitation, *i.e.*, "tertiary structure of the pathogenic self-protein is essentially preserved such that said analog induces an antibody response as evidenced by antibody binding to the unmodified self-protein." *See* Office Action at page 5. As described above, Applicants' specification clearly indicates, and one of ordinary skill would know, recombinant techniques for creating the self-protein analogs of the claims and methods for measuring antibody response as evidenced by antibody binding to an unmodified self-protein.

Second, Applicants have established a correlation between the functional characteristic and the structural characteristics of the claims as amended. As described above, the specification provides the structural features of the claimed self-protein analogs (*e.g.*, substitutions of one or more peptide fragments with a corresponding

number of immunodominant foreign T-cell epitopes) and their correlation with the functional aspects of preserved tertiary structure and antibody response. *See, e.g.*, paragraphs [0031], [0033] and [0037-0038] and Examples 1-9 of the specification. Accordingly, Applicants submit that the written description requirement is met in the present case under Federal Circuit precedent because a functional characteristic is disclosed and a correlation between the function and a structure is disclosed.

Therefore, based on Federal Circuit precedent, Applicants submit that the specification describes the claims as amended in sufficient detail such that one skilled in the art would reasonably conclude that Applicants had possession of the claimed invention. Accordingly, Applicants respectfully request that this rejection be reconsidered and withdrawn.

At page 5 of the Office Action, the Examiner alleges that "[t]here is no support in the specification as originally filed for the method of claim 85 which deletes the term 'tertiary structure of the pathogenic self protein is essentially preserved'." Applicants respectfully disagree. However, solely in an effort to expedite prosecution of the application, Applicants have amended claim 85 to reinstate this language. Accordingly, Applicants respectfully request that this rejection be reconsidered and withdrawn.

At pages 5-6 of the Office Action, the Examiner further alleges that "[t]here is no support in the specification as originally filed for the method of claim 86 which deletes the term 'flanking regions'." Applicants respectfully disagree. However, solely in an effort to expedite prosecution of the application, Applicants have amended claim 86 to reinstate this language. Accordingly, Applicants respectfully request that this rejection be reconsidered and withdrawn.

Rejection under 35 U.S.C. § 112, second paragraph - definiteness

The Examiner rejected claims 85-87 under 35 U.S.C. § 112, second paragraph as allegedly indefinite. *See* Office Action at pages 6-7. Applicants respectfully disagree for the following reasons.

At pages 6-7 of the Office Action, the Examiner rejected claim 85, alleging that the phrase "pathogenic self-protein" is unclear. The specification describes a self-protein as a protein that causes or is capable of causing disease. *See, e.g.*, paragraph [0007] of the specification. Every nuance of the claims does not have to be explicitly described in the specification. *See, e.g., Vas-Cath, Inc. v Mahurkar*, 935 F.2d 1555 at 1563 (Fed. Cir. 1991); *Martin v. Johnson*, 454 F.2d 746, 751 (CCPA 1972) (stating "the description need not be in *ipsis verbis* [*i.e.*, "in the same words"] to be sufficient"). M.P.E.P. § 2163. In view of the disclosure in the present specification, Applicants assert that the phrase "pathogenic self-protein" is definite. Accordingly, Applicants respectfully request that the rejection, as it may apply to the amended claims, be reconsidered and withdrawn.

Rejection under 35 U.S.C. § 102

The Examiner rejected claims 85 and 86 under 35 U.S.C. § 102(b) as allegedly anticipated by Russell-Jones *et al.* (WO 92/05192), as evidenced by Dean *et al.* (U.S. Pat. No. 5,716,596). *See* Office Action at pages 7-9. Applicants respectfully traverse the rejection as it may apply to the claims as amended.

As amended, claim 85 is directed to a method for inducing autoantibodies against a pathogenic self-protein in a subject, said method comprising, among other things, an analog made by substituting one or more peptide fragments in the pathogenic self-protein

with a corresponding number of immunodominant foreign T-cell epitopes such that the tertiary structure of the pathogenic self-protein is essentially preserved such that said analog induces an antibody response as evidenced by antibody binding to the unmodified self-protein. Claim 86 as amended is directed to the method of claim 85, wherein said immunodominant foreign T-cell epitopes are inserted so as to preserve N-terminal and C-terminal flanking regions of amino acid sequences from the original pathogenic self-protein on both sides of the T-cell epitope.

A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference. *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631 (Fed. Cir. 1987); *see also* M.P.E.P. § 2131. The Examiner asserts that Russell-Jones *et al.* teaches that, through the use of recombinant DNA technology, the TraT peptide can be inserted into an immunogen via substituting the TraT peptide for a peptide contained in the immunogen. *See* Office Action at page 7. Applicants maintain that Russell-Jones *et al.* does not disclose an analog of a *self-protein*, but rather replacement of so-called "suppressor regions" in "otherwise immunogenic molecules" such as HIV gp120. This interpretation is supported by page 8, line 36 through page 9, line 3 of Russell-Jones *et al.* which states, in relevant part, "typically, the at least one "immunogen" will be a molecule which is poorly immunogenic, but immunogenic molecules are not excluded." In contrast, the claimed invention is directed to substituting existing regions of self-proteins such that an immune response is generated because the original, self-proteins *are not immunogenic at all.*

At page 8 of the Office Action, the Examiner alleges that there is no evidence of record that the invention of Russell-Jones *et al.* lacks enablement. However, Applicants submit that such evidence is of record in the Declarations of Dr. Travers and Dr. Zinkernagel which conclude that Russell-Jones does not lead or enable one of ordinary skill in the art to arrive at the present invention. *See, e.g.*, paragraph 10 of Dr. Travers' Second Declaration, asserting that the Examiner's application of Russell-Jones *et al.* strains the term "immunogen" well beyond its well-known, ordinary, and art-accepted definition. The Examiner indicates that these Declarations were addressed in previous Office Actions; however, Applicants submit that the Examiner has not responded to the Declarations in view of the amended claims and Applicants' recent responses.

As such, Applicants maintain that, as evidenced by Dean *et al.*, somatostatin is a tetradecapeptide which, in native configuration, is of limited use. *See, e.g.,* Dean *et al.*, col. 1, lines 20-41. Also, as a tetradecapeptide, one could not substitute one or more fragments of somatostatin with a foreign T cell epitope such that the structure of the protein is essentially preserved.

Therefore, since Russell-Jones *et al.*, even as evidenced by Dean *et al.*, does not disclose substitutions of self-proteins such that the tertiary structure is essentially preserved such that said analog induces an antibody response as evidenced by antibody binding to the unmodified self-protein, it does not teach each and every element of the claims as amended. Accordingly, Applicants respectfully request that the rejection be reconsidered and withdrawn.

Rejections under 35 U.S.C. § 103

The Examiner rejected claims 85-87 under 35 U.S.C. § 103(a) as allegedly unpatentable over Russell-Jones *et al.*, in view of Dean *et al.* *See* Office Action at pages 10-12. Applicants respectfully traverse the rejection as it may apply to the claims as amended.

The Examiner bears the burden of establishing a *prima facie* case of obviousness based upon the cited art. *See In re Piasecki*, 745 F.2d 1468, 1471-72 (Fed. Cir. 1984). The factors to be considered under 35 U.S.C. § 103(a), are the scope and content of the prior art; the differences between the prior art and the claims at issue; and the level of ordinary skill in the pertinent art. *See Graham v. John Deere*, 86 S.Ct. 684 (1966) and M.P.E.P. § 2141. This analysis has been the standard for 40 years, and remains the law today. *See KSR International Co v. Teleflex Inc. (KSR)*, 82 USPQ2d 1385 (2007).

The Supreme Court in *KSR* noted that the analysis supporting a rejection under 35 U.S.C. § 103 should be made explicit. *See id.* The Court, quoting *In re Kahn*, 441 F.3d 977, 988 (Fed. Cir. 2006), stated that "[R]ejections on obviousness cannot be sustained by mere conclusory statements; instead there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness." *KSR v. Teleflex*, 550 U.S. at __, 82 USPQ2d at 1396. As outlined in M.P.E.P. § 2141, rationales that may support a conclusion of obviousness include:

(a) combining prior art elements according to known methods to yield predictable results;

(b) simple substitution of one known element for another to obtain predictable results;

(c) use of known technique to improve similar devices (method or product) ready for improvement to yield predictable results;

(d) applying a known technique to a known device (method or product) ready for improvement to yield predictable results;

(e) "obvious to try" – choosing from a finite number of identified, predictable solutions, with a reasonable expectation of success;

(f) known work in the one field of endeavor may prompt variations of it for use in either the same field or a different one based on design incentives or other market forces if the variations are predictable to one of ordinary skill in the art;

(g) some teaching, suggestion, or motivation in the prior art that would have led one of ordinary skill to modify the prior art reference or to combine prior art reference teachings to arrive at the claimed invention.

Applicants respectfully assert that the Examiner has not provided an adequate reason to combine the reference teachings to arrive at Applicants' claimed invention. Furthermore, Applicants respectfully assert that even if the prior art references are combined, the methods do not yield predictable results, as demonstrated by the references themselves.

Applicants respectfully assert that there is no reason in Russell-Jones *et al.*, Dean *et al.* or the general knowledge in the art to combine these references. As mentioned above, since somatostatin is a tetradecapeptide, it cannot be used to make an analog that would retain the necessary tertiary structure to induce autoantibodies. Therefore, rather than support the Examiner's argument, Dean *et al.* actually teaches away from the combination of references. A prior art reference must be considered in its entirety,

including portions that would lead away from the claimed invention. *See* M.P.E.P. § 2141.02(VI) (citing *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540 (Fed. Cir. 1983)); *see also Panduit Corp. v. Dennison Mfg. Co.*, 774 F.2d 1082, 1093-94 (Fed. Cir. 1985) ("The well established rule of law is that each prior art reference must be evaluated as an entirety . . . ."). That is, "[t]here is no suggestion to combine . . . if a reference teaches away from its combination with another source." *Tec Air, Inc. v. Denso Manufacturing Michigan Inc.*, 192 F.3d 1353, 1360 (Fed. Cir. 1999); *see also KSR* at 12 (reaffirming "the corollary principle that when the prior art teaches away from combining certain known elements, discovery of a successful means of combining them is more likely to be nonobvious") (citing United States v. Adams, 383 U.S. 39, 51-52 (1966)). At best, Russell-Jones *et al.* is an invitation to manipulate otherwise immunogenic molecules, and not to manipulate a self-protein, *which is non-immunogenic*, to cause production of autoantibodies when administered to a subject.

As detailed above, Applicants maintain that the Declarations of Dr. Travers and Dr. Zinkernagel conclude that Russell-Jones *et al.* does not lead or enable one of ordinary skill in the art to arrive at the present invention. (The Examiner indicates that these Declarations were addressed in previous Office Actions; however, Applicants submit that the Examiner has not responded to the Declarations in view of the amended claims and Applicants' recent responses.) As such, Applicants maintain, as evidenced by Dean *et al.*, somatostatin is a tetradecapeptide which, in native configuration, is of limited use and one could not substitute one or more fragments of somatostatin with a foreign T-cell epitope such that the structure of the protein is essentially preserved.

Thus, Applicants respectfully assert that the cited references do not render the claimed invention obvious. Moreover, Applicants remind the Examiner of the Declarations of Mr. Schmidt and Mr. Borregaard which provide additional evidence of the technical, commercial and financial success of the invention sufficient to rebut a *prima facie* case of obviousness. *See, e.g.*, the Declarations submitted on October 9, 2000 and May 23, 2002. Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw this rejection.

In addition, the Examiner rejected claim 101 under 35 U.S.C. § 103(a) as allegedly unpatentable over Russell-Jones *et al.*, in view of Dean *et al.* and further in view of Hellman (WO 93/05810) and Le *et al.* (U.S. Patent No. 5,698,195). *See* Office Action at pages 12-13. Applicants respectfully traverse the rejection as it may apply to the claims as amended.

For the reasons detailed above, Applicants respectfully assert that there is no reason in Russell-Jones *et al.*, Dean *et al.* or the general knowledge in the art to combine these references. Applicants maintain that the Declarations of Dr. Travers and Dr. Zinkernagel conclude that Russell-Jones *et al.* does not lead or enable one of ordinary skill in the art to arrive at the present invention. (The Examiner indicates that these Declarations were addressed in previous Office Actions; however, Applicants submit that the Examiner has not responded to the Declarations in view of the amended claims and Applicants' recent responses.) As such, Applicants maintain, as evidenced by Dean *et al.*, somatostatin is a tetradecapeptide which, in native configuration, is of limited use and one could not substitute one or more fragments of somatostatin with a foreign T-cell

epitope such that the structure of the protein is essentially preserved. Hellman and Le *et al.* fail to remedy the deficiencies of Russell-Jones *et al.* and Dean *et al.*

Thus, Applicants respectfully assert that the cited references do not render the claimed invention obvious. Moreover, Applicants remind the Examiner of the Declarations of Mr. Schmidt and Mr. Borregaard which provide additional evidence of the technical, commercial and financial success of the invention sufficient to rebut a *prima facie* case of obviousness. *See, e.g.*, the Declarations submitted on October 9, 2000 and May 23, 2002. Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw this rejection.

Conclusion

All of the stated grounds of rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding rejections and that they be withdrawn. Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

Respectfully submitted,

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